NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 446

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 1-TRANS-DELTA^9-TETRAHYDROCANNABINOL

(CAS NO. 1972-08-3)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk anlayses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

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P.O. Box 12233
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CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

P.C. Chan, Ph.D., Study Scientist
G.A. Boorman, D.V.M., Ph.D.
D.A. Bridge, B.S.
J.R. Bucher, Ph.D.
M.R. Elwell, D.V.M., Ph.D.
T.J. Goehl, Ph.D.
J.K. Haseman, Ph.D.
G.N. Rao, D.V.M., Ph.D.
J.H. Roycroft, Ph.D.
R.C. Sills, D.V.M., Ph.D.
G.S. Travlos, D.V.M.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

SRI International
Conducted 13- and 22-week studies, evaluated pathology findings

T.A. Jorgenson, M.S., Principal Investigator
E.F. Meierhenry, Ph.D.
R.J. Spanggord, Ph.D.

TSI Mason Research Institute
Conducted 2-year studies, evaluated pathology findings

A.G. Braun, Sc.D., Principal Investigator
F.A. Voelker, M.S., D.V.M.
M.E.P. Goad, D.V.M., Ph.D.

Experimental Pathology Laboratories, Inc.
Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
B.F. Hamilton, D.V.M., Ph.D.

Dynamac Corporation
Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides, prepared pathology report on rats (13 October 1992)

J.C. Seely, D.V.M., Chairperson
PATHCO, Inc.
D. Dixon, D.V.M., Ph.D.
National Toxicology Program
J.R. Hailey, D.V.M.
National Toxicology Program
B.F. Hamilton, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
C.C. Shackelford, D.V.M., M.S., Ph.D.
National Toxicology Program
R.C. Sills, D.V.M., Ph.D.
National Toxicology Program

Evaluated slides, prepared pathology report on mice (30 July 1992)

J.C. Seely, D.V.M., Chairperson
PATHCO, Inc.
R. Cattley, V.M.D., Ph.D.
Chemical Industry Institute of Toxicology
B.F. Hamilton, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
C.C. Shackelford, D.V.M., M.S., Ph.D.
National Toxicology Program
R.C. Sills, D.V.M., Ph.D.
National Toxicology Program

Analytical Sciences, Inc.
Provided statistical analyses

R.W. Morris, M.S, Principal Investigator
N.G. Mintz, B.S.
S. Rosenblum, M.S.

Biotechnical Services, Inc.
Prepared Technical Report

D.D. Lambright, Ph.D., Principal Investigator
S.R. Gunnels, M.A.
T.A. King-Hunter, B.S.
T.L. Rhoades, B.S.

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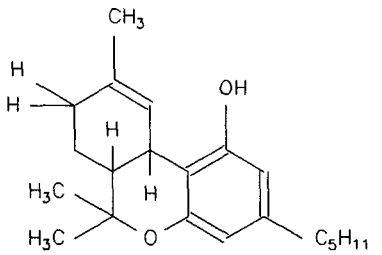
ABSTRACT



1-TRANS-DELTA^9-TETRAHYDROCANNABINOL

CAS No. 1972-08-3

Chemical Formula: $C_{21}H_{30}O_2$ Molecular Weight: 314.5

Synonyms: 3-Pentyl-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6h-dibenzo(b,d)pyran-1-ol; delta^1-tetrahydrocannabinol; (–)-delta^1-3,4-trans-tetrahydrocannabinol; delta^9-tetrahydrocannabinon; THC; delta^1-THC; delta^9-THC
Trade names: Dronabinol; Marinol

1-Trans-delta^9-tetrahydrocannabinol (THC) was nominated by the National Cancer Institute to the NTP for study because it is the major psychoactive component of marijuana and a widely used Schedule I substance. Male and female F344/N rats and B6C3F$_1$ mice received THC (97% pure) in corn oil by gavage for 13 weeks, 13 weeks with a 9-week recovery period, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and mouse peripheral blood cells.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats received 0, 5, 15, 50, 150, or 500 mg THC/kg body weight in corn oil by gavage, 5 days per week for 13 weeks. Six male and six female rats receiving 500 mg/kg died before the end of the study. The final mean body weights and weight gains of all dosed groups of males and females, except 5 mg/kg females, were significantly lower than those of the controls. Feed consumption by dosed groups was similar to that by controls. Clinical findings observed during the study included lethargy, sensitivity to touch, convulsions, tremors, and aggressiveness. There were no clinical pathology differences considered to be directly related to the administration of THC. The absolute and relative uterus weights of 50, 150, and 500 mg/kg females were significantly lower than those of the controls. Treatment-related multifocal atrophy was observed in the testes of 150 and 500 mg/kg males; uterine and ovarian hypoplasia observed in 150 and 500 mg/kg females was also considered to be related to THC administration. Based on final mean body weights and mortality observed in the 13-week study, doses selected for the 2-year rat study were 12.5, 25, and 50 mg/kg.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice received 0, 5, 15, 50, 150, or 500 mg THC/kg body weight in corn oil by gavage, 5 days per week for 13 weeks. There were no treatment-related deaths. The final mean body weight and weight gain of 500 mg/kg males were significantly lower than those of the controls. Clinical findings included lethargy and aggressiveness, and both male and female mice in all dosed groups were easily startled. There were no absolute or relative organ weight differences, clinical pathology differences, or microscopic changes observed that were considered to be related to the administration of THC. Due to the minimal THC-related effects

observed in the 13-week study, doses selected for the 2-year mouse study were 125, 250, and 500 mg/kg.

13-Week with 9-Week Recovery Study in Rats

Groups of 10 male and 10 female rats received 0, 5, 15, 50, 150, or 500 mg THC/kg body weight in corn oil by gavage, 5 days per week for 13 weeks, and then were allowed to recover during a 9-week treatment-free period. Five male and eight female 500 mg/kg rats, five male and two female 150 mg/kg rats, and three male and two female 50 mg/kg rats died before the end of the study. During the 13-week dosing period, mean body weight gains of all dosed groups of rats were lower than those of the controls but returned to normal during the recovery period. Final mean body weights of all dosed groups were similar to those of the controls. Clinical findings observed during the recovery period included sensitivity to touch, convulsions, and aggressiveness. The absolute right testis weight of 500 mg/kg males was significantly lower than that of the controls. Treatment-related multifocal atrophy of the testis was observed in 150 and 500 mg/kg males. There were no treatment-related lesions observed in females administered THC.

13-Week with 9-Week Recovery Study in Mice

Groups of 10 male and 10 female mice received 0, 5, 15, 50, 150, or 500 mg THC/kg body weight in corn oil by gavage, 5 days per week for 13 weeks, and then were allowed to recover during a 9-week treatment-free period. The final mean body weights of all dosed groups were similar to those of the controls. Clinical findings observed during the study included lethargy and aggressiveness, and both male and female mice in all dosed groups were easily startled. The absolute and relative uterus weights of 150 and 500 mg/kg female mice were significantly lower than those of the controls, as was the absolute uterus weight of 50 mg/kg females.

2-Year Study in Rats

Groups of 62 vehicle control male rats, 60 low-dose male rats, 70 mid- and high-dose male rats, and 60 female rats were administered 0, 12.5, 25, or 50 mg THC/kg body weight in corn oil by gavage for 104 to 105 weeks. Nine or ten animals from each group were evaluated at 15 months.

Survival, Body Weights, and Clinical Findings

Survival of all dosed groups was generally significantly greater than that of the controls. Mean body weights of dosed groups of males and females were lower than those of the controls throughout the study. Convulsions and seizures were observed in all dosed groups of male and female rats, usually following dosing or handling.

Hematology and Clinical Chemistry

At the 15-month interim evaluation, total leukocyte and lymphocyte counts in all dosed groups of females were greater than those of the controls, and platelet counts in these groups were lower than that of the controls. Levels of follicle stimulating and luteinizing hormones in all dosed groups of males were significantly greater than those of the controls, as was the serum corticosterone level of 25 mg/kg females.

Pathology Findings

No increased incidences of neoplasms were considered related to administration of THC. The incidences of mammary gland fibroadenoma and uterine stromal polyps were decreased in dosed groups of females, as were the incidences of pituitary gland adenomas, interstitial cell adenomas of the testis, and pancreatic adenomas in dosed males.

2-Year Study in Mice

Groups of 62 vehicle control male mice, 60 low-dose male mice, 61 mid-dose male mice, and 60 high-dose male mice and 60 female mice were administered 0, 125, 250, or 500 mg THC/kg body weight in corn oil by gavage for 104 to 105 weeks (males) or 105 to 106 weeks (females).

Survival, Body Weights, and Clinical Findings

Survival of 500 mg/kg males was significantly less than that of the controls; survival of all other groups of males and of all dosed groups of females was similar to that of the controls. Mean body weights of all dosed groups were markedly lower than those of the controls throughout the study. Clinical findings in dosed groups included hyperactivity, convulsions, and seizures which occurred following dosing or handling.

Hematology

At the 15-month interim evaluation, total leukocyte and lymphocyte counts in all dosed groups of males were significantly lower than those of the controls.

Pathology Findings

Increased incidences of thyroid gland follicular cell adenoma occurred in 125 mg/kg males and females, but the increase was not dose-related. Increased incidences of thyroid gland follicular cell hyperplasia occurred in all dosed groups of males and females. Increased incidences of forestomach hyperplasia and ulcers occurred in all groups of males administered THC. Incidences of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined) occurred with a significant negative trend in male and female mice, as did incidences of eosinophilic foci and fatty change in the liver.

GENETIC TOXICOLOGY

THC was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 with or without rat and hamster liver S9 fractions. In cultured Chinese hamster ovary cells, THC induced sister chromatid exchanges at the highest dose tested in the presence of S9; at this dose level, cell cycle delay indicative of toxicity was observed. THC did not induce chromosomal aberrations in cultured Chinese hamster ovary cells with or without S9 metabolic activation enzymes. *In vivo*, no increase in the frequency of micronucleated erythrocytes was observed in the peripheral blood of male or female mice administered THC by gavage for 13 weeks.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of 1-trans-delta^9-tetrahydrocannabinol in male or female F344/N rats administered 12.5, 25, or 50 mg/kg. There was *equivocal evidence of carcinogenic activity* of THC in male and female B6C3F$_1$ mice based on the increased incidences of thyroid gland follicular cell adenomas in the 125 mg/kg groups.

Increased incidences of thyroid gland follicular cell hyperplasia occurred in male and female mice, and increased incidences of hyperplasia and ulcers of the forestomach were observed in male mice.

The incidences of mammary gland fibroadenomas and uterine stromal polyps were decreased in dosed groups of female rats, as were the incidences of pancreatic adenomas, pituitary gland adenomas, and interstitial cell adenomas of the testis in dosed male rats and liver neoplasms in dosed mice. These decreases were likely related to lower body weights in dosed animals.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 1-Trans-Delta^9-Tetrahydrocannabinol

Variable	Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses	0, 12.5, 25, or 50 mg/kg in corn oil by gavage	0, 12.5, 25, or 50 mg/kg in corn oil by gavage	0, 125, 250, or 500 mg/kg in corn oil by gavage	0, 125, 250, or 500 mg/kg in corn oil by gavage
Body weights	Dosed groups lower than controls	Dosed groups lower than controls	Dosed groups lower than controls	Dosed groups lower than controls
2-Year survival rates	22/52, 35/51, 33/52, 31/52	23/51, 40/51, 33/51, 32/50	50/62, 53/60, 45/61, 34/60	47/60, 50/60, 44/60, 41/60
Nonneoplastic effects	None	None	Forestomach: hyperplasia (7/62, 33/58, 38/58, 18/56); ulcer (5/62, 17/58, 14/58, 8/56) Thyroid gland (follicular cell): hyperplasia (16/62, 48/60, 45/61, 27/57)	Thyroid gland (follicular cell): hyperplasia (28/60, 46/60, 40/60, 33/60)
Neoplastic effects	None	None	None	None
Uncertain findings	None	None	Thyroid gland (follicular cell): adenoma (0/62, 6/60, 3/61, 1/57)	Thyroid gland (follicular cell): adenoma (4/60, 9/60, 3/60, 1/60)
Decreased incidences	Pancreas: adenoma (8/52, 0/51, 2/52, 0/52); Pituitary gland: adenoma (21/52, 19/51, 14/51, 9/52); Testis: interstitial cell adenoma (46/52, 40/51, 36/52, 43/52)	Mammary gland: fibroadenoma (15/51, 11/51, 11/51, 8/50); Uterus: stromal polyp (8/51, 5/51, 2/51, 2/50)	Liver: hepatocellular adenoma (25/62, 11/60, 6/61, 2/57); hepatocellular adenoma or carcinoma (31/62, 13/60, 9/61, 3/57); eosinophilic foci (18/62, 1/60, 0/61, 0/57); fatty change (20/62, 11/60, 1/61, 1/57)	Liver: hepatocellular adenoma (17/60, 9/60, 7/59, 3/60); hepatocellular adenoma or carcinoma (22/60, 14/60, 11/59, 4/60); eosinophilic foci (9/60, 0/60, 1/59, 1/60); fatty change (13/60, 3/60, 0/59, 2/60)
Level of evidence of carcinogenic activity	No evidence	No evidence	Equivocal evidence	Equivocal evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Positive with S9; negative without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Micronucleated erythrocytes	
Mouse peripheral blood *in vivo*:	No increase in frequency observed

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on 1-trans-delta^9-tetrahydrocannabinol on June 21, 1994, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

Arnold L. Brown, M.D., Chairperson
University of Wisconsin Medical School
Madison, WI

Paul T. Bailey, Ph.D.
Environmental and Health Sciences Laboratory
Mobil Oil Corporation
Princeton, NJ

Meryl H. Karol, Ph.D.
Department of Environmental Occupational Health
University of Pittsburgh
Pittsburgh, PA

Curtis D. Klaassen, Ph.D., Principal Reviewer
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Claudia S. Miller, M.D.
University of Texas Health Sciences Center
San Antonio, TX

Janardan K. Reddy, M.D.
Department of Pathology
Northwestern University Medical School
Chicago, IL

Irma Russo, M.D.
Fox Chase Cancer Center
Philadelphia, PA

Louise Ryan, Ph.D.
Division of Biostatistics
Harvard School of Public Health and
Dana-Farber Cancer Institute
Boston, MA

Robert E. Taylor, M.D., Ph.D., Principal Reviewer
Department of Pharmacology
Howard University College of Medicine
Washington, DC

Matthew J. van Zwieten, D.V.M., Ph.D., Principal Reviewer
Department of Safety Assessment
Merck Research Laboratories
West Point, PA

Mary Jo Vodicnik, Ph.D.
Lilly MSG Development Center
Belgium

Jerrold M. Ward, D.V.M., Ph.D.
National Cancer Institute
Frederick, MD

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 21, 1994, the draft Technical Report on the toxicology and carcinogenesis studies of 1-trans-delta^9-tetrahydrocannabinol (THC) received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. P.C. Chan, NIEHS, introduced the toxicology and carcinogenesis studies of THC by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on chemical-related neoplasm and nonneoplastic lesion incidences. He also presented toxicokinetic data for male rats. The proposed conclusions were *no evidence of carcinogenic activity* in male and female F344/N rats and *equivocal evidence of carcinogenic activity* in male and female B6C3F$_1$ mice.

Dr. Klaassen, a principal reviewer, agreed with the proposed conclusions. He asked for a table in the discussion outlining decreases in neoplasm incidences and the correlation of these decreases with body weights. Dr. Chan said a table would be added. Dr. Klaassen asked why a 9-week recovery period was included in the present studies. Dr. Chan said that the effects of THC linger, so a recovery period was included to study the effects of the chemical, particularly on the reproductive system, and to aid in possible extrapolation of the effects in humans.

Dr. Taylor, the second principal reviewer, agreed with the proposed conclusions. Dr. Taylor asked for an expansion of the discussion of arachidonic acid metabolism modification by THC, noting it would be helpful to indicate the extent and direction and the possible therapeutic or physiologic implications. Dr. Chan agreed (page 17). Dr. Taylor said a comment explaining the selection of gavage as the route of administration should be added to the report, noting that this route differs from the typical routes of human exposure. Dr. Chan said that insufficient compound was available to perform an inhalation study, intraperitoneal injection was less akin to human routes of exposure, and only a small historical database exists for the intraperitoneal injection route.

Dr. van Zwieten, the third principal reviewer, agreed with the proposed conclusions. He asked for comments on the apparent inverse dose-response relationship for the thyroid gland neoplasm incidences in mice (page 76).

Dr. Ward asked if step sectioning of mouse thyroid glands had been considered in view of the equivocal findings. Dr. M.R. Elwell, NIEHS, said that because of the small size of the gland, one cross-section is fairly representative of the entire organ. Dr. Ward asked if lower body weights of dosed groups could have been caused by exceeding maximum tolerated doses. Dr. J.R. Bucher, NIEHS, said that because THC can affect weight gain, the possibility of exceeding the maximum tolerated dose would be difficult to interpret. Dr. Chan added that because THC is taken up and stored in adipose tissue, THC buildup during chronic administration could cause the maximum tolerated dose to be exceeded. Dr. Russo asked for comments on the lower serum levels of follicle stimulating hormone and luteinizing hormone in female rats and mice when compared to male rats and mice. Dr. Bucher said although the reproductive effects of THC were well studied, there was no explanation for the difference in the hormone levels in males and females in the present studies. Dr. van Zwieten noted that many decreased neoplasm incidences observed in dosed groups were within historical control ranges from 2-year NTP gavage studies. Dr. Miller suggested including data contrasting human and animal THC plasma levels and including levels typically achieved in humans to discourage the concept of THC as a cancer inhibitor. Dr. Bucher noted that the results of these studies could be misinterpreted to demonstrate that exposure to THC could provide beneficial therapeutic effects and added that the NTP has attempted to stress that most of the observed changes were due to decreased weight gain.

Dr. Klaassen cited a report in the text that the amount of THC taken in by habitual marijuana smokers was estimated to range from 0.3 to 12.0 mg/kg, which would be comparable to doses administered to rats in the present studies. Dr. Taylor pointed out that plasma levels resulting from a dose administered via inhalation would be much higher than those resulting from the same dose administered orally.

Dr. Klaassen moved that the Technical Report on 1-trans-delta^9-tetrahydrocannabinol be accepted with the revisions discussed and the conclusions as written for male and female rats, *no evidence of carcinogenic activity*, and for male and female mice, *equivocal evidence of carcinogenic activity.* Dr. Bailey seconded the motion, which was accepted unanimously with eleven votes.